

Electronic Supporting Information

Osthol and curcumin as inhibitors of human Pgp and multidrug efflux pumps of *Staphylococcus aureus*: Reversing the resistance against frontline antibacterial drugs

Prashant Joshi,^{a,b} Samsher Singh,^{b,c} Abubakar Wani,^d Sadhana Sharma,^{b,d} Shreyans K. Jain,^{b,e} Baljinder Singh,^{b,e} Bishan D. Gupta,^e Naresh K. Satti,^e Surrinder Koul,^f Inshad A. Khan,^{b,*} c Ajay Kumar,^{d,*} Sandip B. Bharate,^{a,b,*} and Ram A. Vishwakarma^{a,b,e,*}

^a Medicinal Chemistry Division, Indian Institute of Integrative Medicine (CSIR), Canal Road, Jammu-180001, India

^b Academy of Scientific & Innovative Research (AcSIR), Indian Institute of Integrative Medicine (CSIR), Canal Road, Jammu-180001, India

^c Clinical Microbiology Division, Indian Institute of Integrative Medicine (CSIR), Canal Road, Jammu-180001, India

^d Cancer Pharmacology Division, Indian Institute of Integrative Medicine (CSIR), Canal Road, Jammu-180001, India

^e Natural Products Chemistry Division, Indian Institute of Integrative Medicine (CSIR), Canal Road, Jammu-180001, India

^f Bioorganic Chemistry Division, Indian Institute of Integrative Medicine (CSIR), Canal Road, Jammu-180001, India

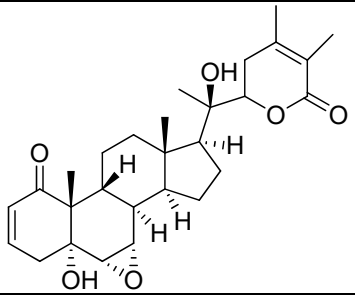
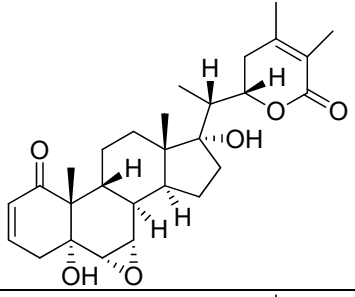
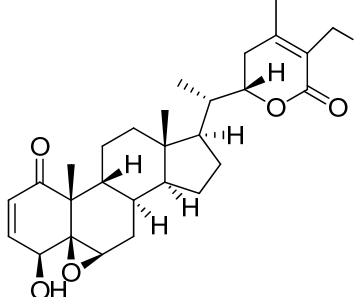
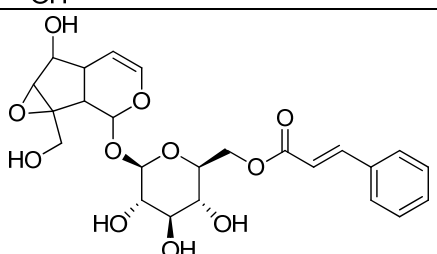
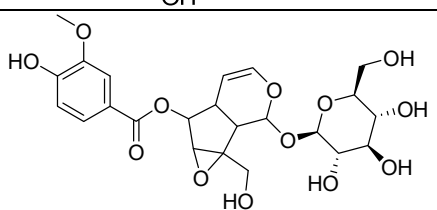
*E-mail: ram@iiim.res.in (R.A.V.); sbharate@iiim.res.in (S.B.B.);
ajaykmahajan@hotmail.com (A.K.); iakhan@iiim.ac.in (I.A.K.)

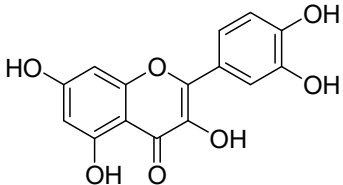
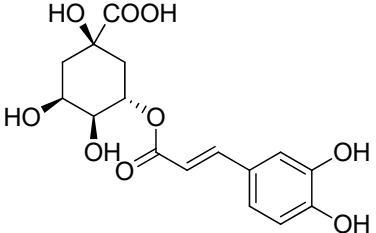
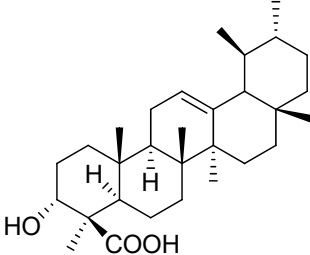
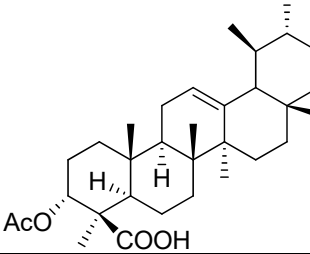
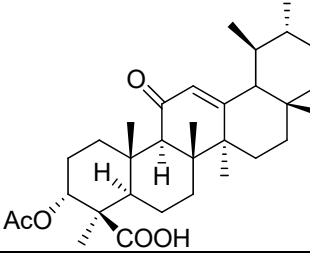
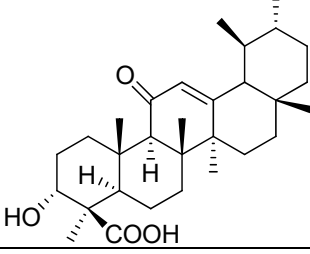
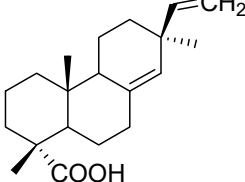
CONTENTS

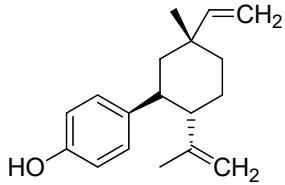
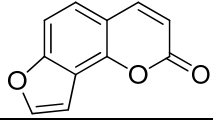
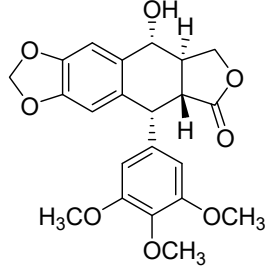
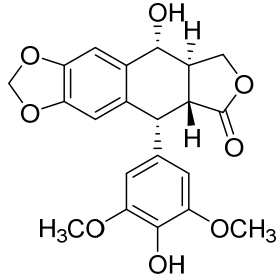
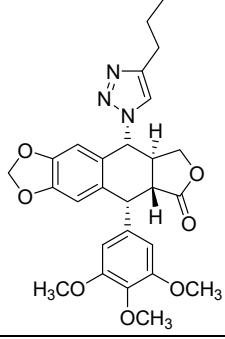
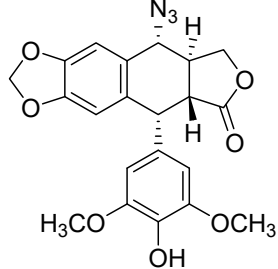
S1. Pgp screening results of 302 compounds

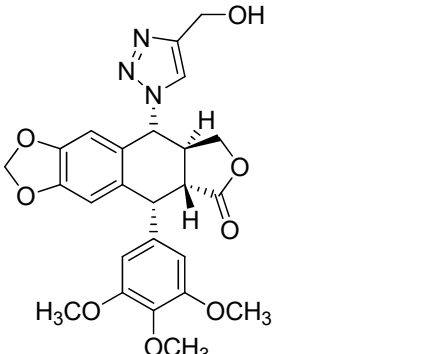
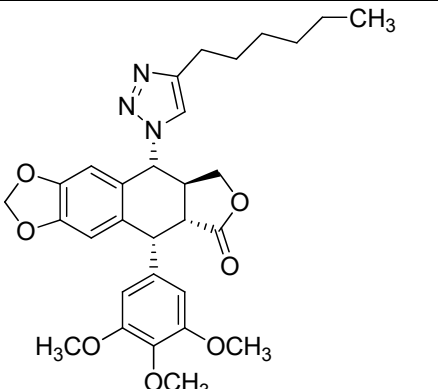
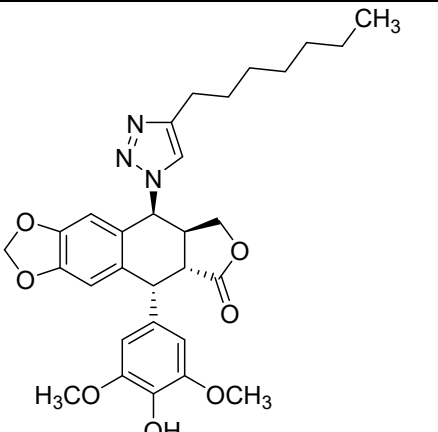
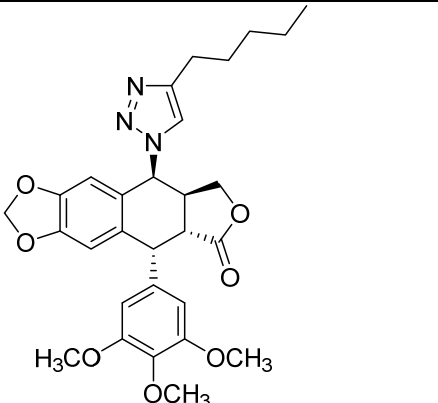
S1. Pgp screening results of 302 compounds^a

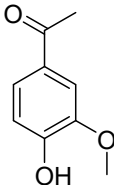
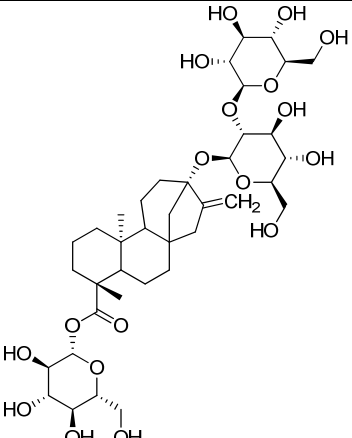
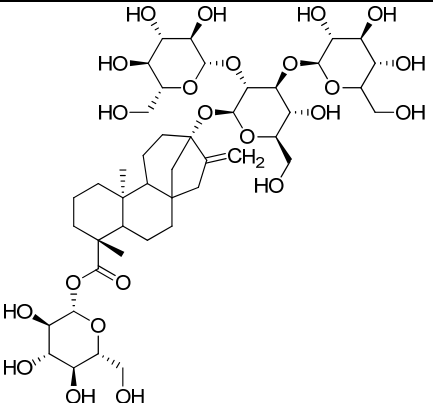
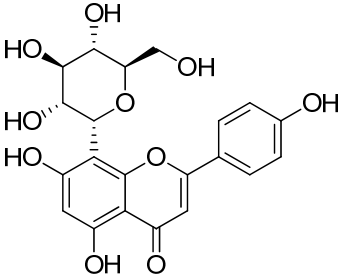
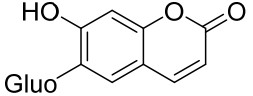
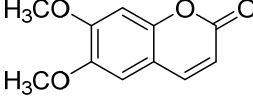
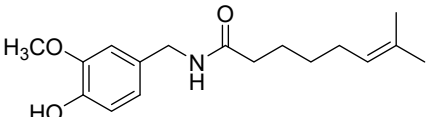
Table S1: Structures, codes, mol. wt. and % Rh123 accumulated in LS180 cells

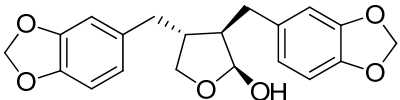
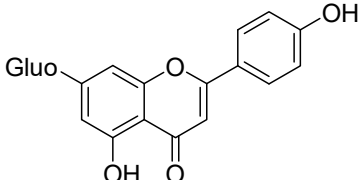
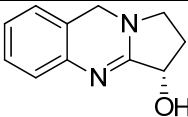
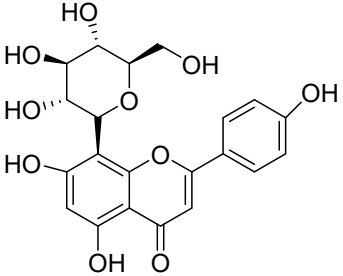
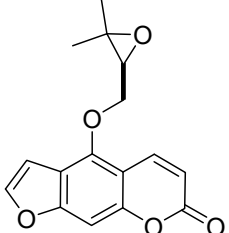
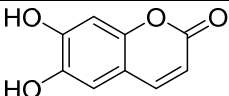
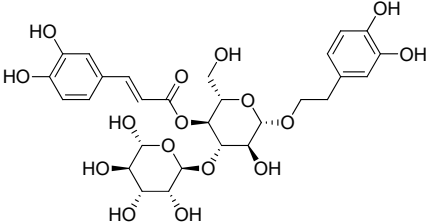
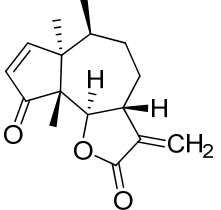
S. no.	Structure	Codes	Mol. Wt.	% Rh123 accumulated in LS 180 cells
1		IN00002	470.60	86.1
2		IN00003	470.60	126.3
3		IN00004	470.60	86.0
4		IN00005	492.47	91.9
5		IN00006	512.46	76.9

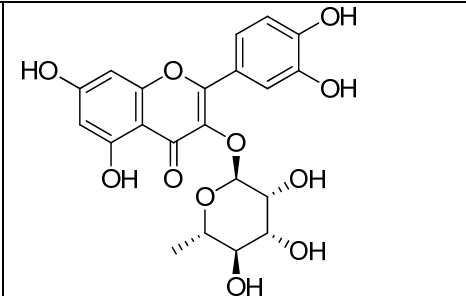
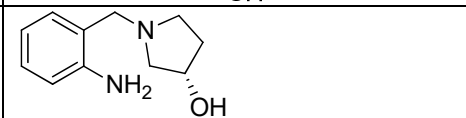
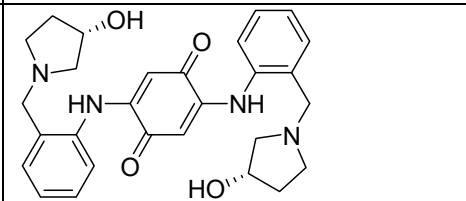
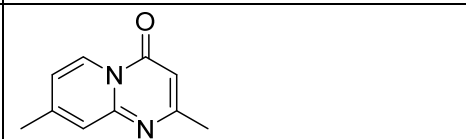
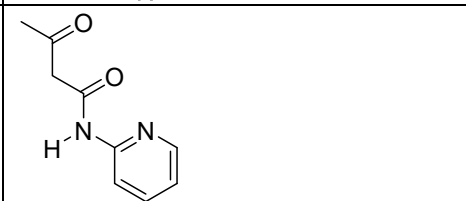
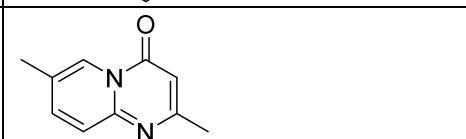
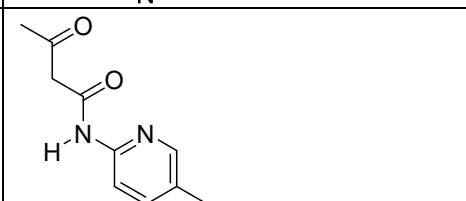
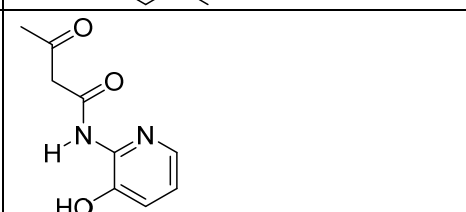
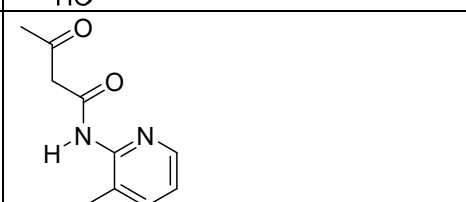
6		IN00007	302.24	69.9
7		IN00008	354.31	67.4
8		IN00009	456.70	106.3
9		IN00010	498.74	101.8
10		IN00011	512.72	75.6
11		IN00012	470.68	75.6
12		IN00016	304.47	70.1

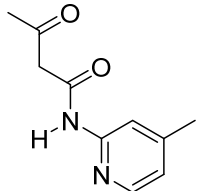
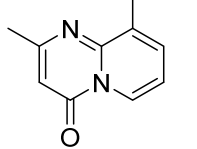
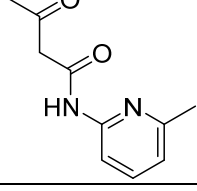
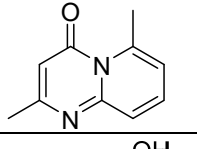
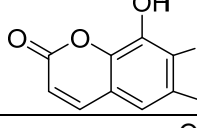
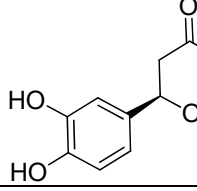
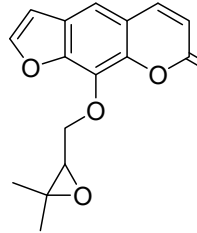
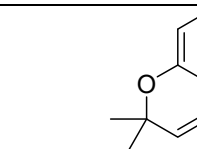
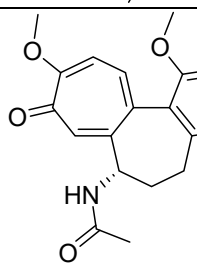
13		IN00018	256.38	90.6
14		IN00020	186.16	75.9
15	 <p>Podophyllotoxin</p>	IN00021	414.41	75.4
16		IN00022	400.38	72.6
17		IN00023	507.55	65.1
18		IN00024	426.40	68.1

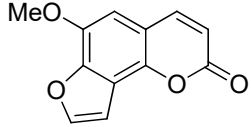
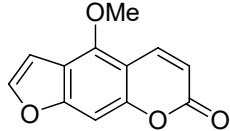
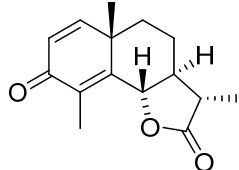
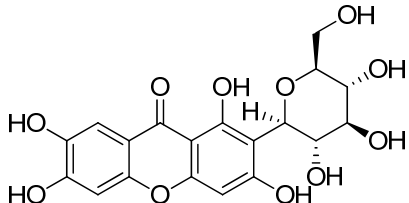
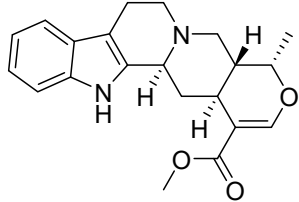
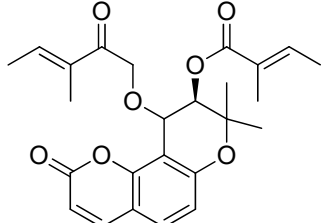
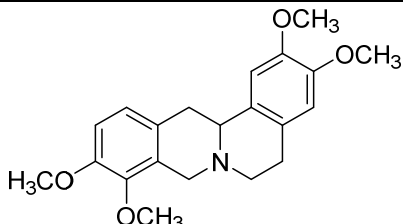
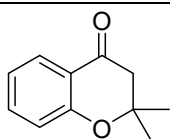
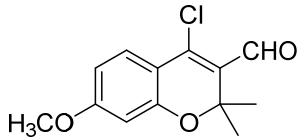
19		IN00025	495.48	120.7
20		IN00026	549.61	111.9
21		IN00027	549.61	103.0
22		IN00038	535.59	100.6

23		IN00039	166.17	71.4
24		IN00040	804.87	58.7
25		IN00041	967.01	89.8
26		IN00042	432.38	73.4
27	 Gluo	IN00043	161.13	91.9
28	 Scoparone	IN00044	206.19	81.3
29		IN00045	291.39	96.0

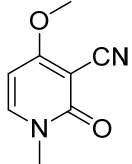
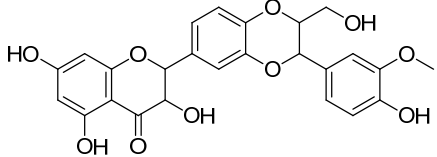
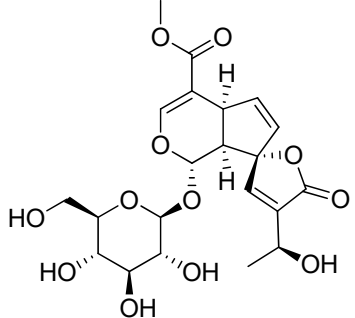
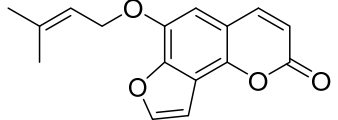
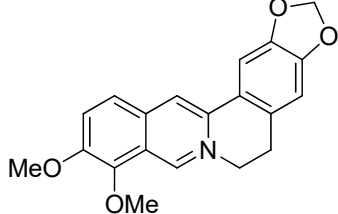
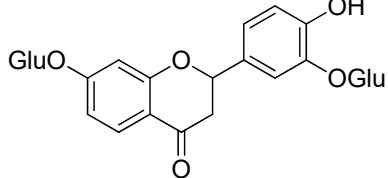
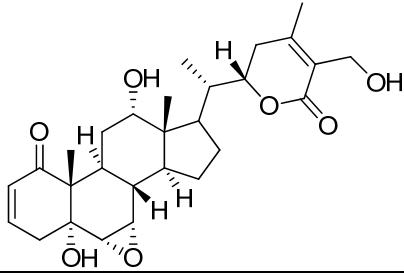
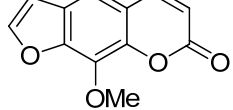
30		IN00046	356.37	79.4
31		IN00047	253.23	101.4
32		IN00048	188.23	68.3
33		IN00049	432.38	83.8
34		IN00051	286.28	64.5
35		IN00052	178.14	56.5
36		IN00053	624.59	38.9
37		IN00054	260.33	131.6

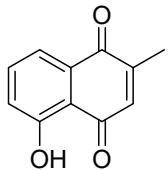
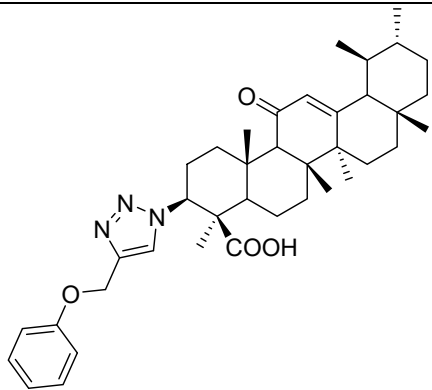
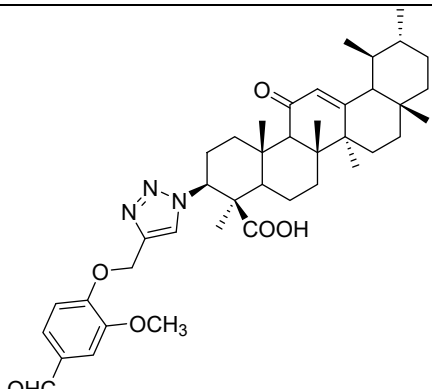
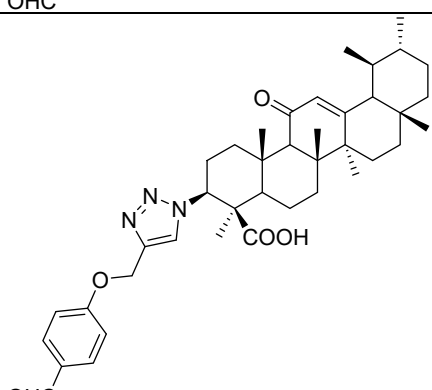
38		IN00056	448.38	127.5
39		IN00057	192.26	136.0
40		IN00070	488.58	125.5
41		IN00071	174.20	124.9
42		IN00072	178.19	139.1
43		IN00073	174.20	82.5
44		IN00074	192.21	101.5
45		IN00075	194.19	88.5
46		IN00076	192.21	88.7

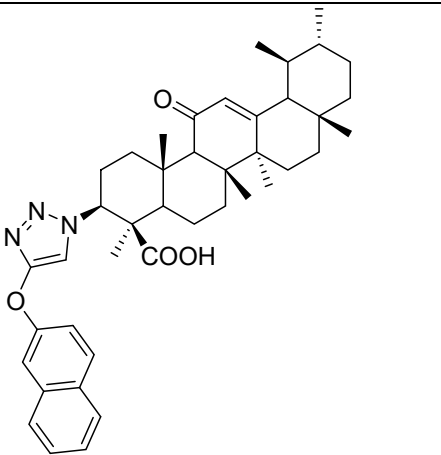
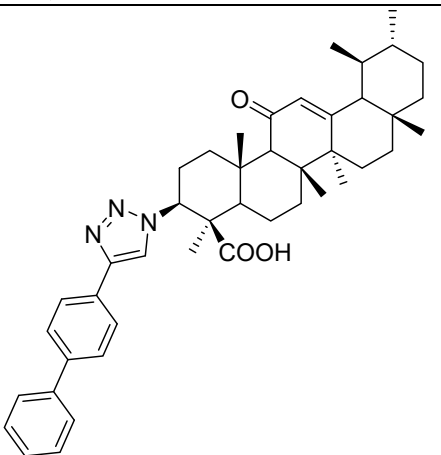
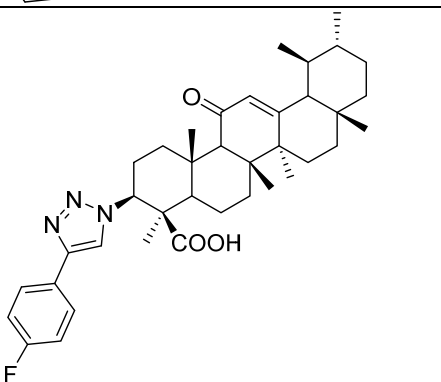
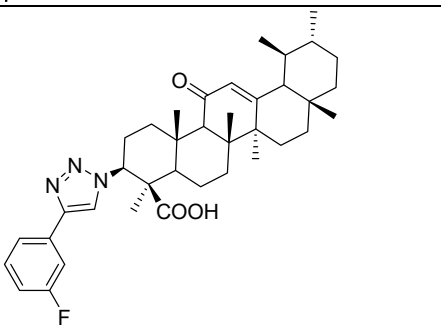
47		IN00077	192.21	133.3
48		IN00078	174.20	82.8
49		IN00079	192.21	134.6
50		IN00080	174.20	129.0
51		IN00081	202.16	126.6
52		IN00082	272.25	114.0
53		IN00084	286.28	129.7
54		IN00085	228.2433+B68	116.8
55		IN00086	385.41	80.4

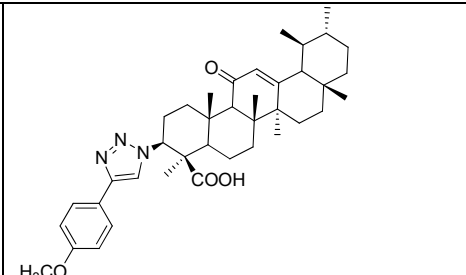
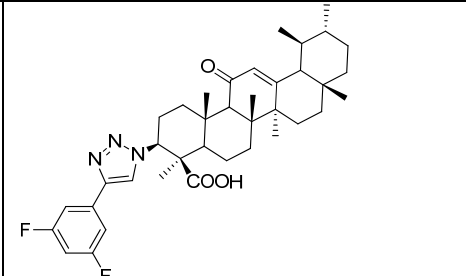
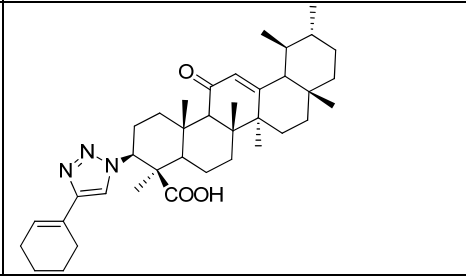
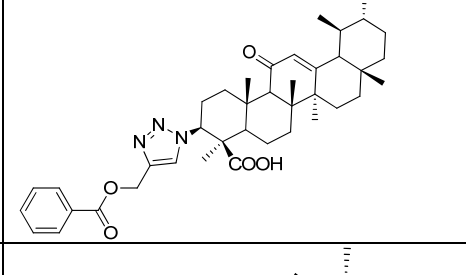
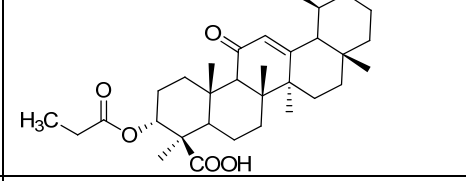
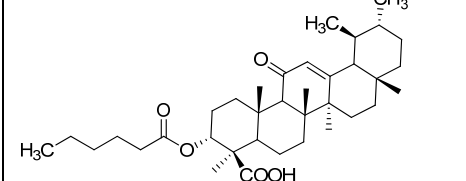
56	 Sphondin	IN00087	216.19	72.9
57		IN00088	216.19	62.3
58		IN00089	246.30	57.6
59		IN00090	422.34	60.4
60		IN00091	352.43	41.2
61		IN00093	426.49	219.0
62		IN00094	355.43	66.0
63		IN00095	176.21	47.8
64		IN00096	252.69	54.1

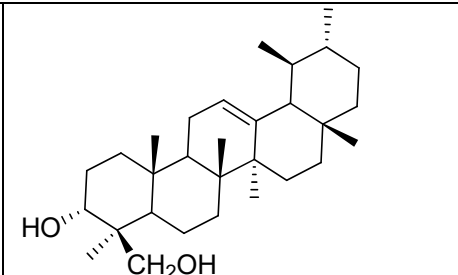
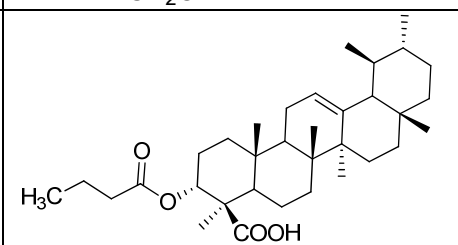
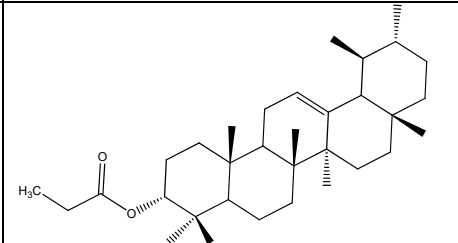
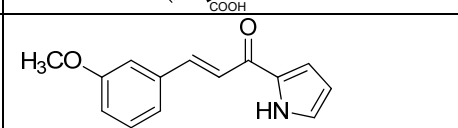
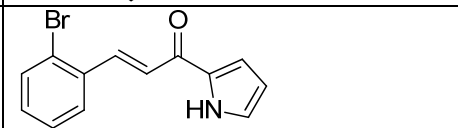
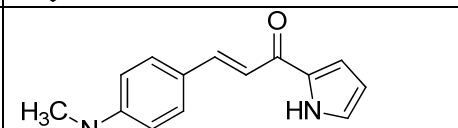
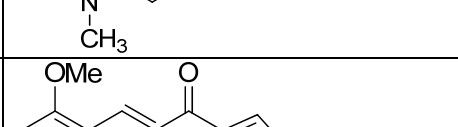
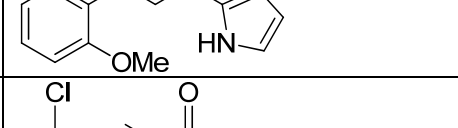
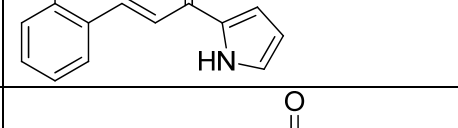
65		IN00097	278.30	72.0
66		IN00098	250.29	65.1
67		IN00099	450.44	87.9
68		IN00100	494.49	71.8
69		IN00101	286.24	68.7
70		IN00102	285.34	108.3
71		IN00103	312.32	89.5
72		IN00104	332.39	86.5

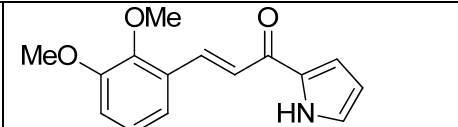
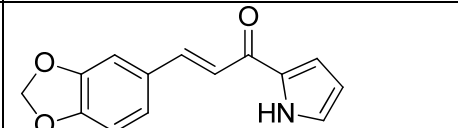
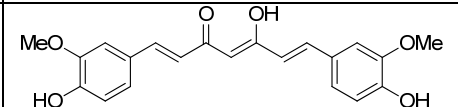
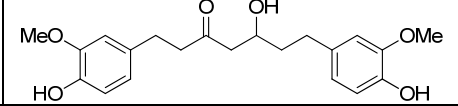
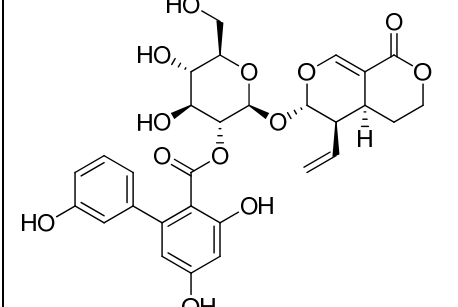
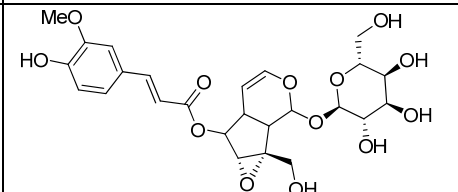
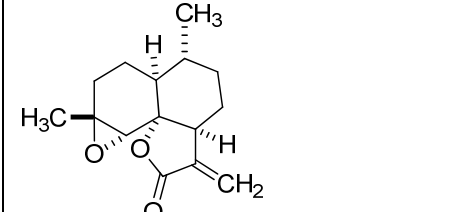
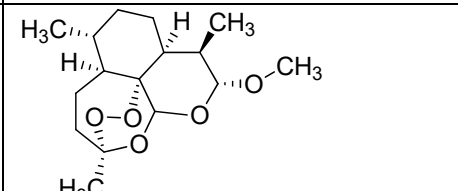
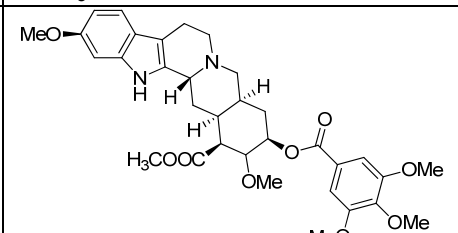
73		IN00105	164.16	96.7
74	 Racemic form	IN00106	482.44	93.2
75		IN00107	470.42	58.9
76		IN00108	270.28	81.4
77		IN00109	372.82	85.7
78		IN00110	384.36	53.2
79		IN00112	486.60	97.6
80		IN00113	216.19	84.2

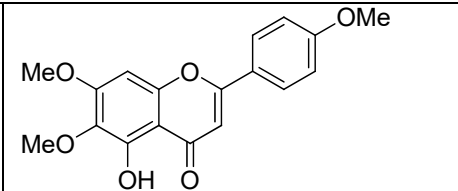
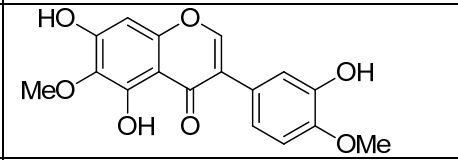
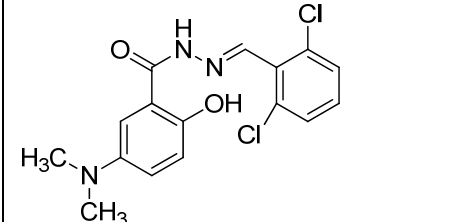
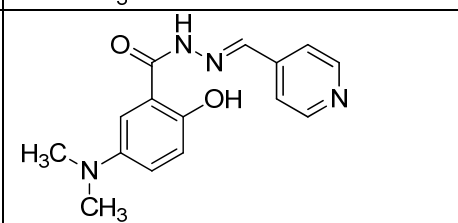
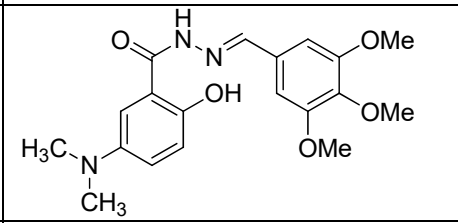
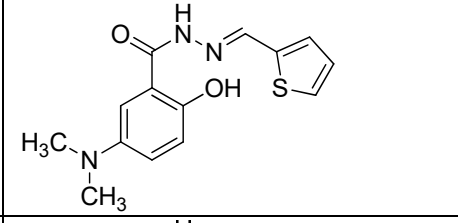
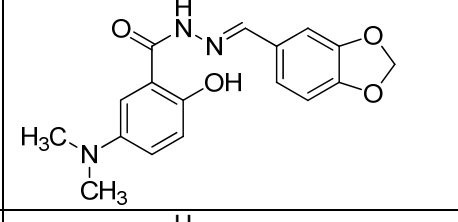
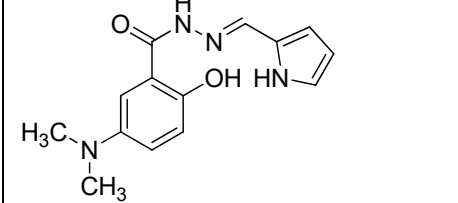
81		IN00114	188.18	90.3
82		IN00116	627.86	75.6
83		IN00117	685.89	82.5
84		IN00118	655.87	98.7

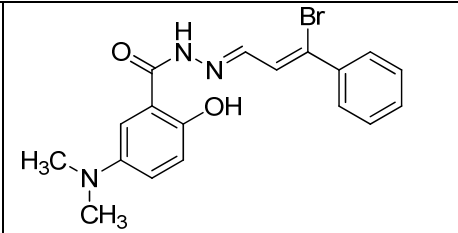
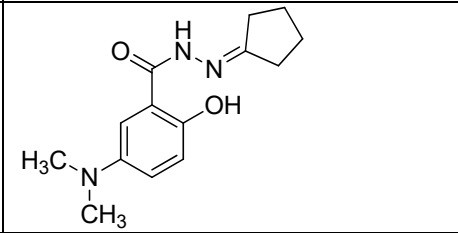
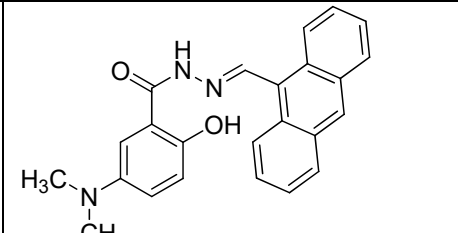
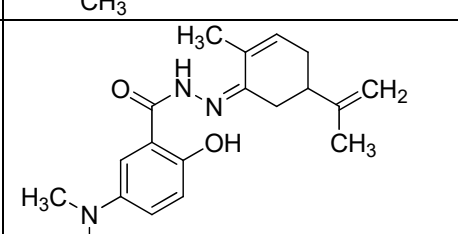
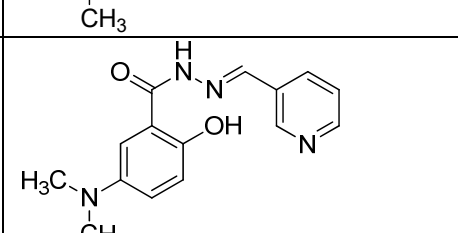
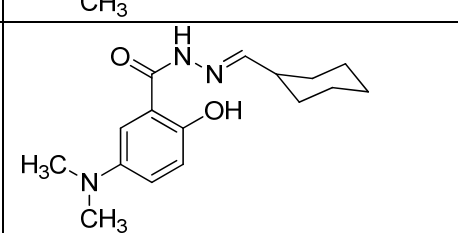
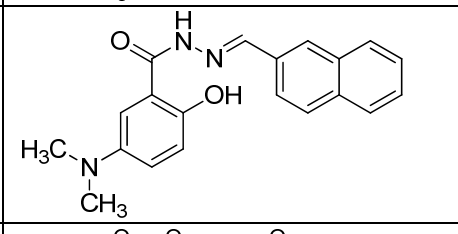
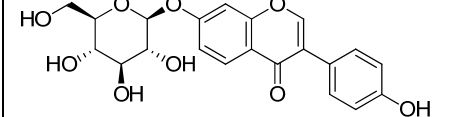
85		IN00119	663.89	40.6
86		IN00120	673.93	80.0
87		IN00121	615.82	35.0
88		IN00122	615.82	62.0

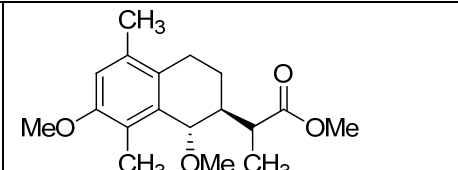
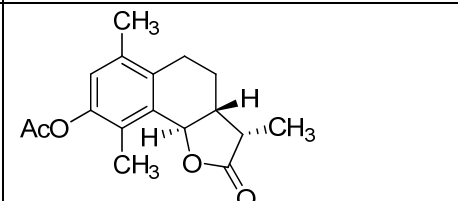
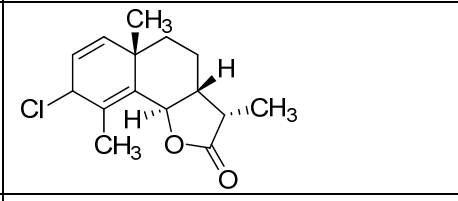
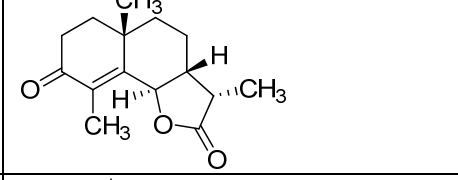
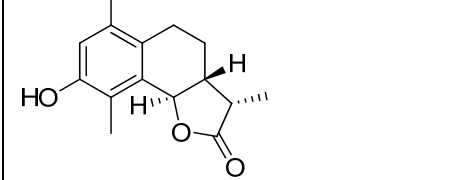
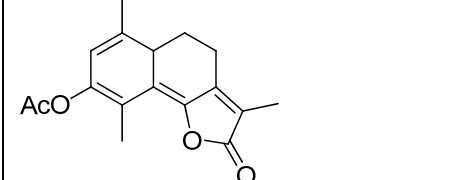
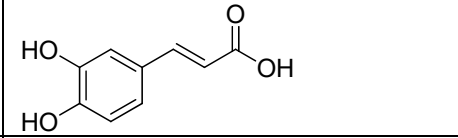
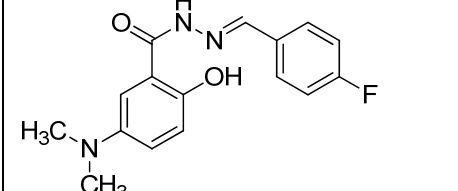
89		IN00123	627.86	91.9
90		IN00124	633.81	51.5
91		IN00125	601.86	61.8
92		IN00126	655.87	85.6
93		IN00127	526.75	79.9
94		IN00128	568.83	79.9

95		IN00129	442.72	98.3
96		IN00131	526.79	111.2
97		IN00132	512.76	67.1
98		IN00133	227.26	80.9
99		IN00134	276.13	99.1
100		IN00135	240.30	37.8
101		IN00136	257.28	112.7
102		IN00138	231.68	127.2
103		IN00139	227.26	105.5

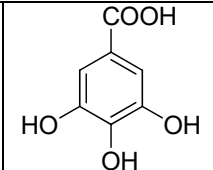
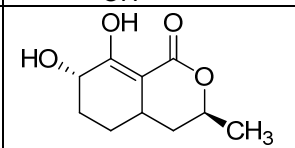
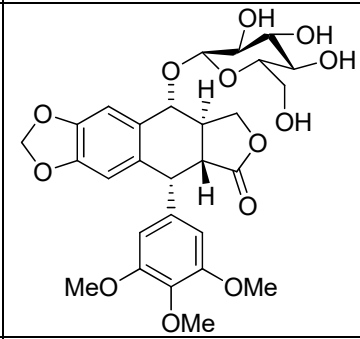
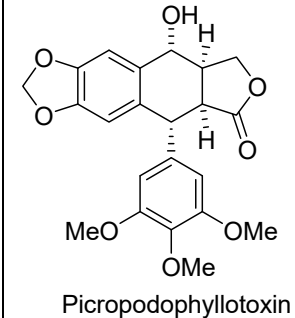
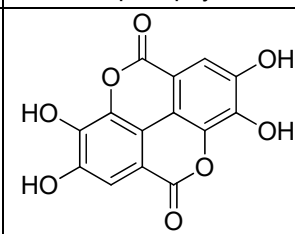
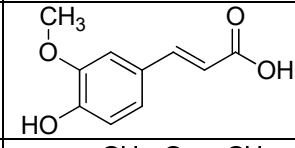
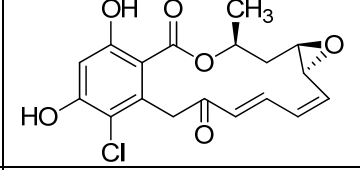
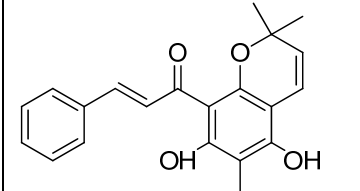
104		IN00140	257.28	43.8
105		IN00141	241.24	118.7
106		IN00142	368.38	169.9
107		IN00143	374.43	129.8
108		IN00144	584.57	82.6
109		IN00145	538.50	108.7
110		IN00146	248.32	70.1
111		IN00147	298.37	73.3
112		IN00149	608.68	68.2

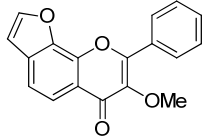
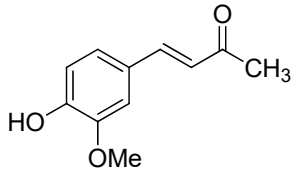
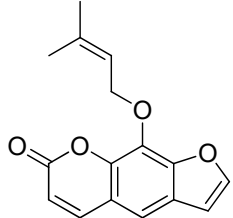
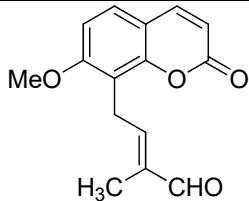
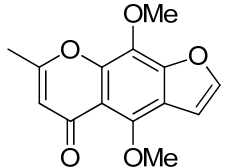
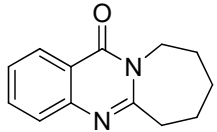
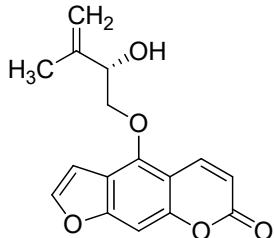
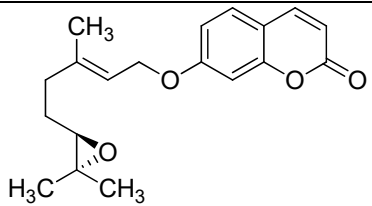
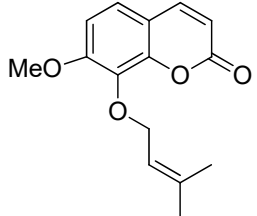
113		IN00150	328.32	66.8
114		IN00151	330.29	96.0
115		IN00153	352.22	103.6
116		IN00154	284.31	85.9
117		IN00155	373.40	89.9
118		IN00156	289.35	93.9
119		IN00157	327.33	76.4
120		IN00158	272.30	73.3

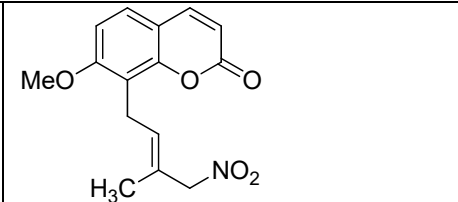
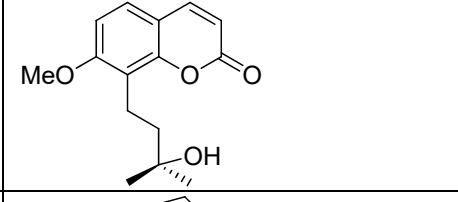
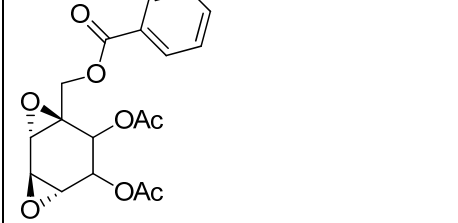
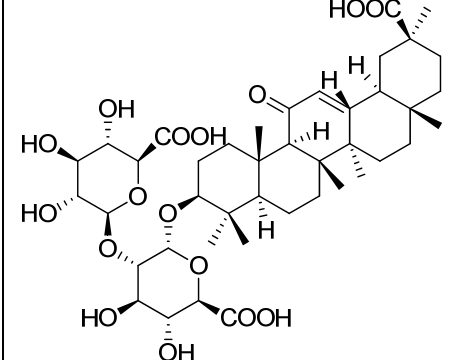
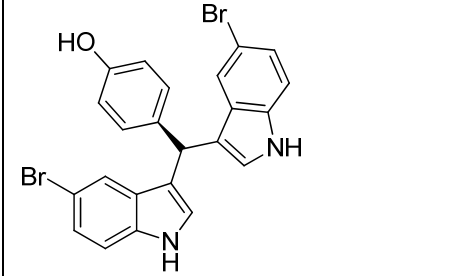
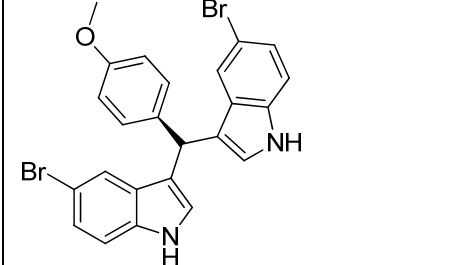
121		IN00159	388.26	100.6
122		IN00160	261.32	74.3
123		IN00161	383.44	132.5
124		IN00162	327.42	83.0
125		IN00163	284.31	71.9
126		IN00164	289.37	106.5
127		IN00165	333.38	101.8
128		IN00166	416.38	103.7

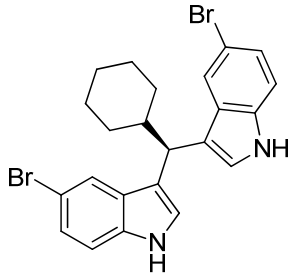
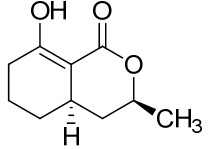
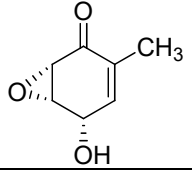
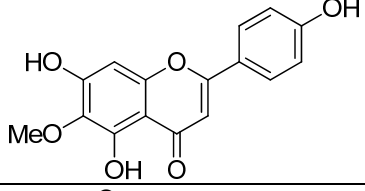
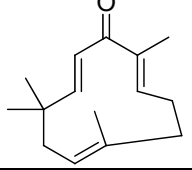
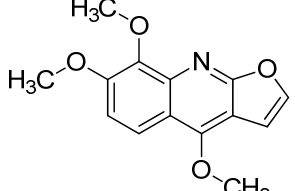
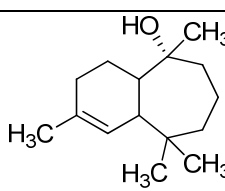
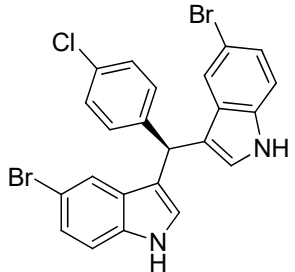
129		IN00167	306.40	111.6
130		IN00168	288.34	99.4
131		IN00169	266.76	114.6
132		IN00170	248.32	105.0
133		IN00171	246.30	103.5
134		IN00172	286.32	112.9
135		IN00175	180.16	110.7
136		IN00176	301.32	119.3

137		IN00177	329.44	121.5
138		IN00178	275.35	142.7
139		IN00179	324.33	98.4
140		IN00180	289.37	100.4
141		IN00181	273.33	79.7
142		IN00182	301.38	106.4
143		IN00183	275.34	90.8
144		IN00184	301.34	117.7
145		IN00185	301.38	91.5
146		IN00186	247.29	107.8

147		IN00187	170.12	88.7
148		IN00188	198.22	81.4
149		IN00189	576.55	70.5
150	 <p>Picropodophyllotoxin</p>	IN00190	414.41	80.7
151		IN00191	302.19	88.3
152		IN00192	194.18	79.4
153		IN00193	362.80	93.3
154		IN00194	338.40	68.1

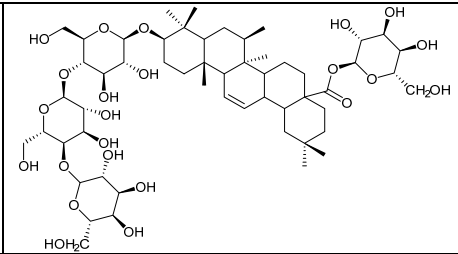
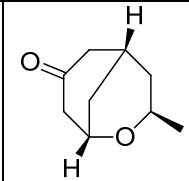
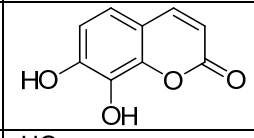
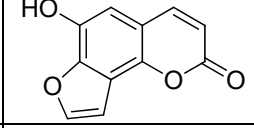
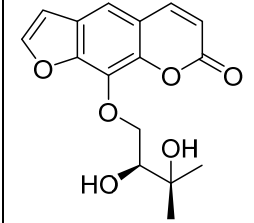
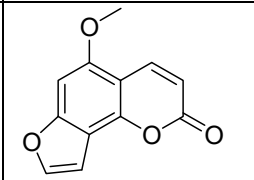
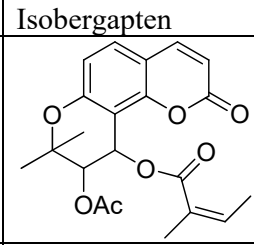
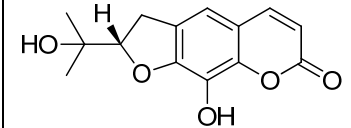
155		IN00195	294.30	71.0
156		IN00196	192.21	79.5
157		IN00197	270.28	217.9
158		IN00198	258.27	81.9
159		IN00199	302.45	56.5
160		IN00200	214.26	79.3
161		IN00201	286.28	73.9
162		IN00202	314.38	95.0
163		IN00203	244.29	246.2

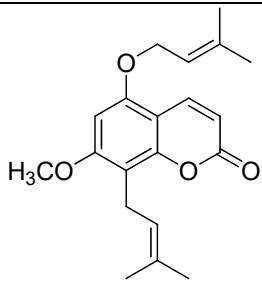
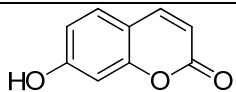
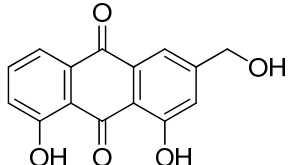
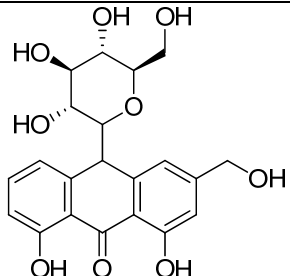
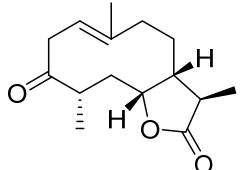
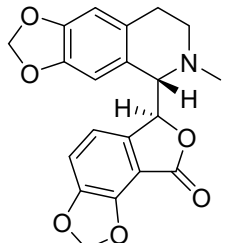
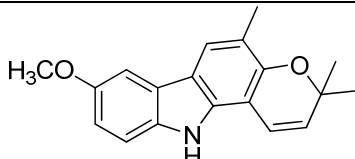
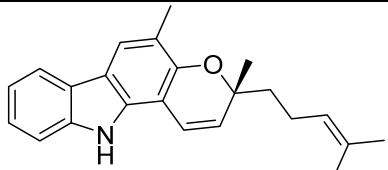
164		IN00204	290.29	78.4
165		IN00205	262.30	63.1
166		IN00206	362.33	78.5
167		IN00207	822.93	99.7
168		IN00208	496.19	136.8
169		IN00209	540.25	94.9

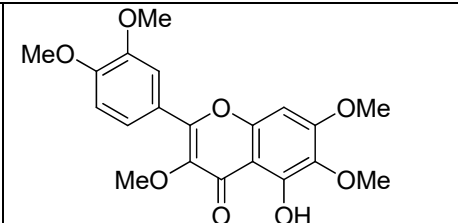
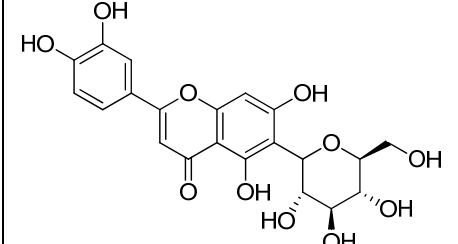
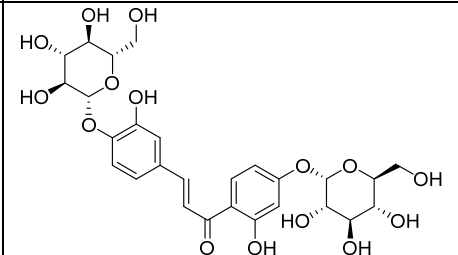
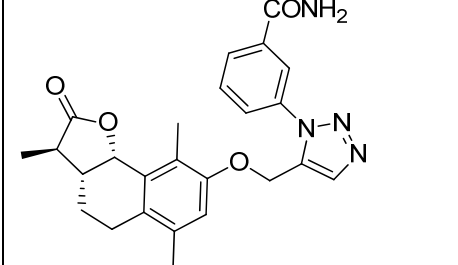
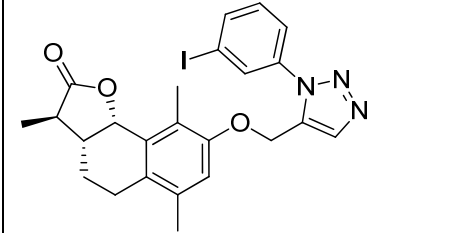
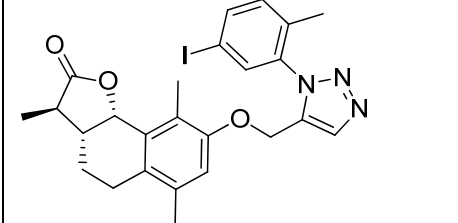
170		IN00210	486.24	94.6
171		IN00211	182.22	77.4
172		IN00212	140.14	93.3
173		IN00214	300.26	88.7
174		IN00215	218.33	108.8
175		IN00216	259.26	60.4
176		IN00217	222.37	89.2
177		IN00219	514.64	81.7

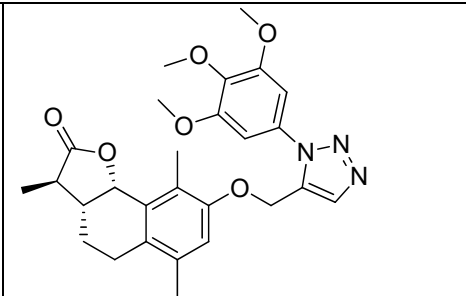
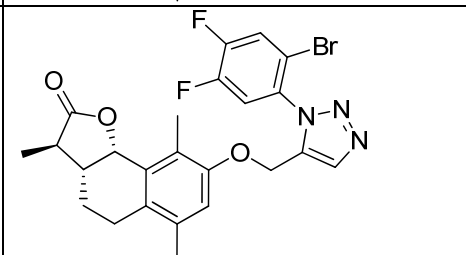
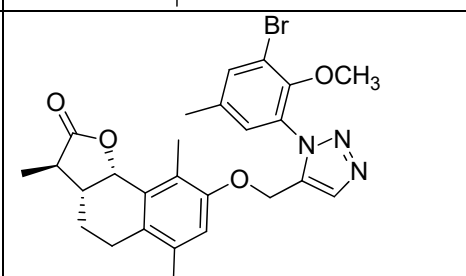
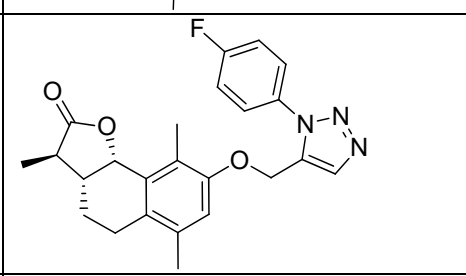
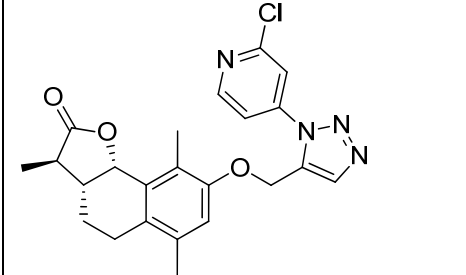
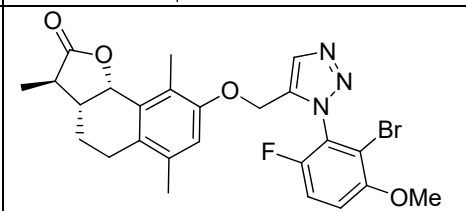
178		IN00220	589.12	77.5
179		IN00221	633.81	76.7
180		IN00225	408.53	59.6
181		IN00226	360.36	94.2
182		IN00227	330.42	83.6
183		IN00228	231.25	98.0
184		IN00229	379.41	39.0
185		IN00230	231.25	70.1
186		IN00231	240.26	99.8

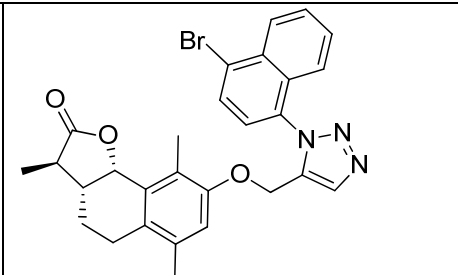
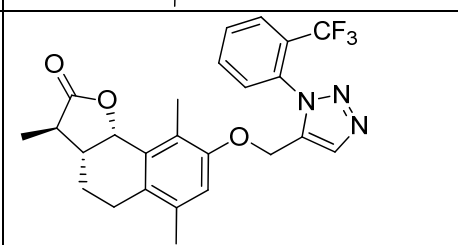
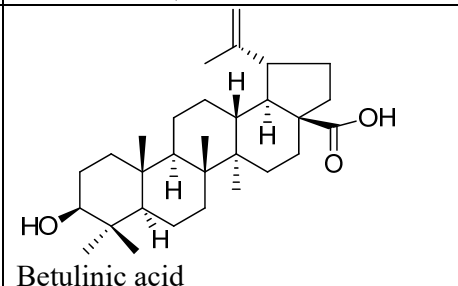
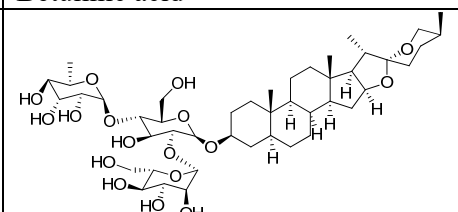
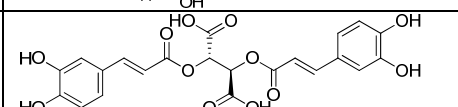
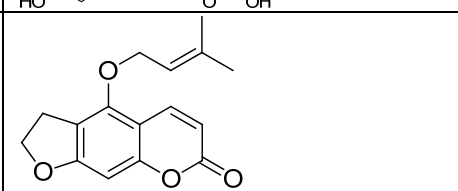
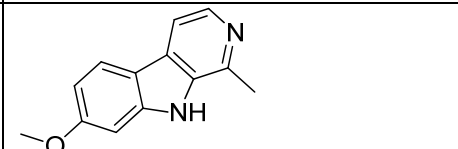
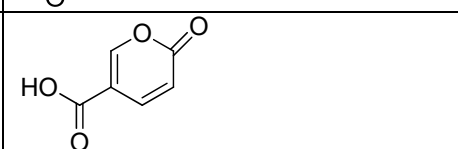
187		IN00232	290.31	75.0
188		IN00234	290.31	68.4
189		IN00235	330.33	263.6
190 ^b	 Coumurrayin	IN00236	274.31	101.1
191		IN00237	288.30	71.0
192		IN00238	246.26	168.4
193		IN00239	290.31	94.0
194		IN00240	274.31	95.7

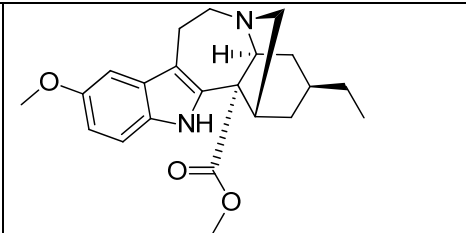
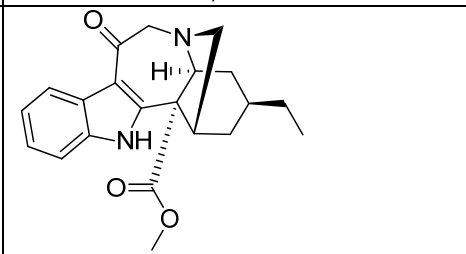
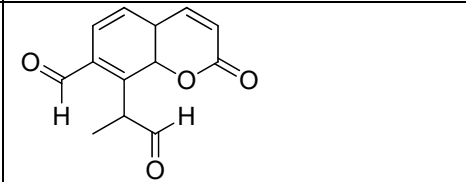
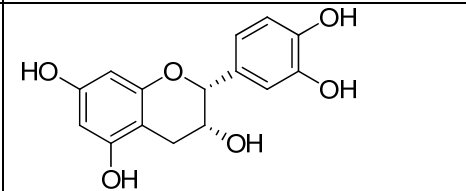
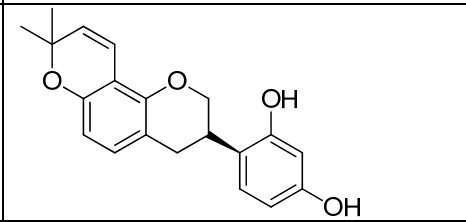
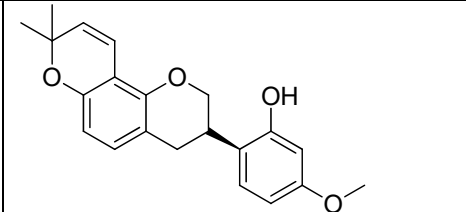
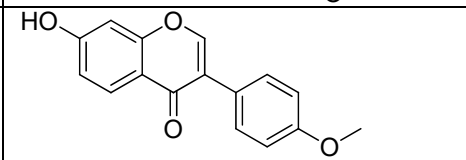
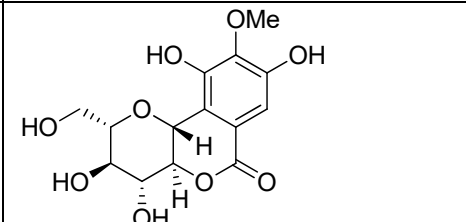
195		IN00243	1105.26	109.3
196		IN00244	154.21	95.1
197		IN00245	178.14	73.6
198		IN00246	202.16	72.6
199		IN00247	304.29	79.6
200	 Isobergapten	IN00248	216.19	84.4
201		IN00249	386.40	119.0
202		IN00250	262.26	93.1

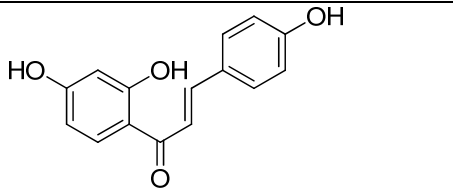
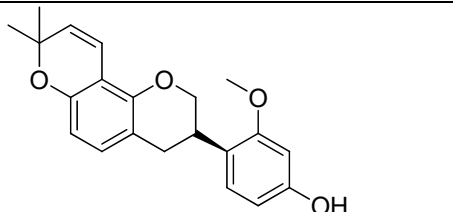
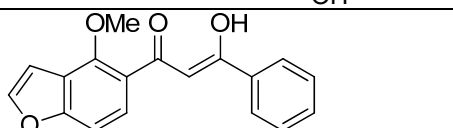
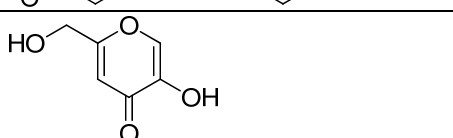
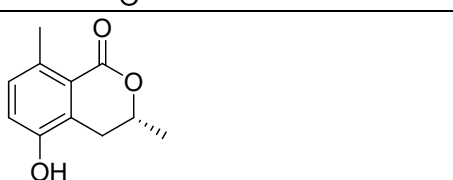
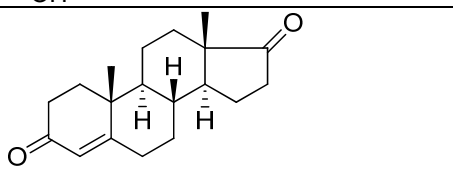
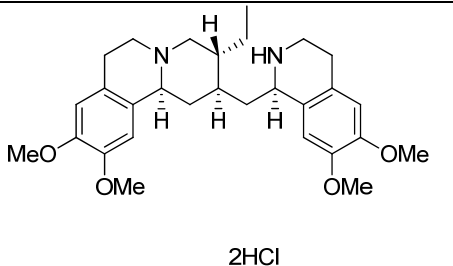
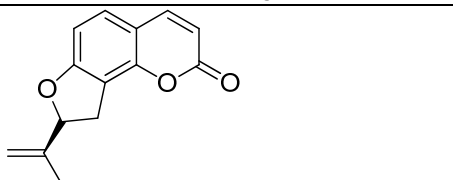
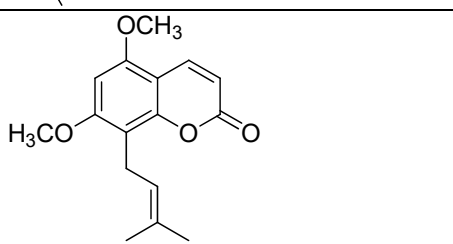
203	 <p>Sesibiricin</p>	IN00251	328.40	105.0
204		IN00252	162.14	100.9
205		IN00253	270.24	85.1
206		IN00255	418.39	83.6
207		IN00256	250.33	68.7
208		IN00257	367.35	72.3
209		IN00258	293.36	76.1
210		IN00259	331.45	75.0

211		IN00260	388.37	86.0
212		IN00261	448.38	87.2
213		IN00262	596.53	83.5
214		IN00263	446.50	93.4
215		IN00264	529.37	73.6
216		IN00265	543.40	78.8

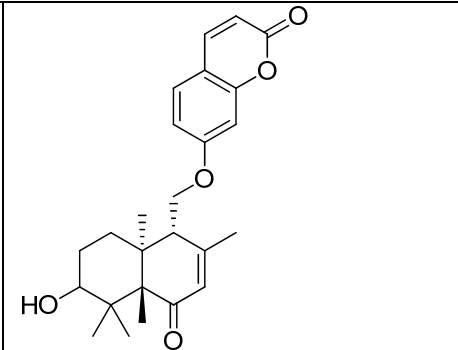
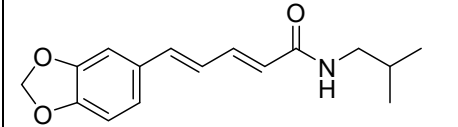
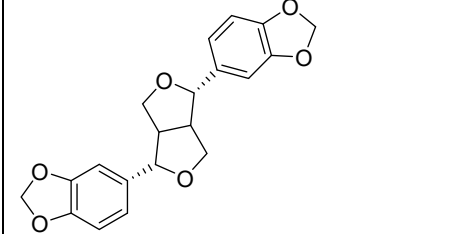
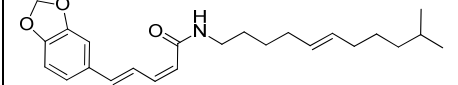
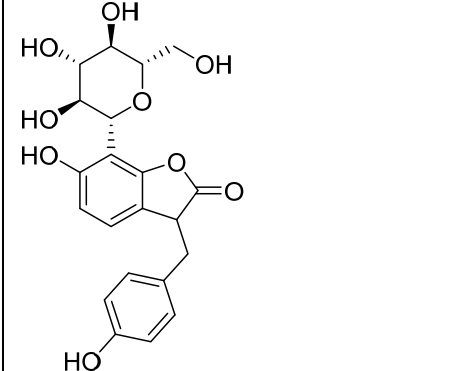
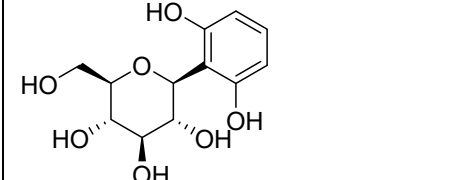
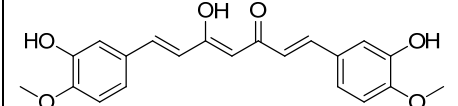
217		IN00266	493.55	87.1
218		IN00267	518.35	102.9
219		IN00268	526.42	77.6
220		IN00269	421.46	72.9
221		IN00270	438.91	106.1
222		IN00271	530.39	77.7

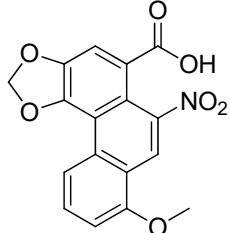
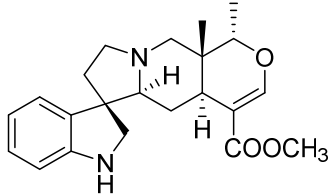
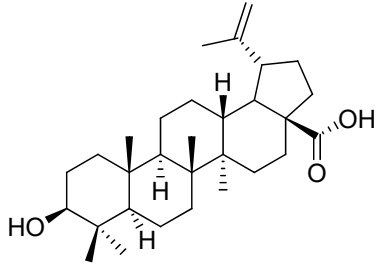
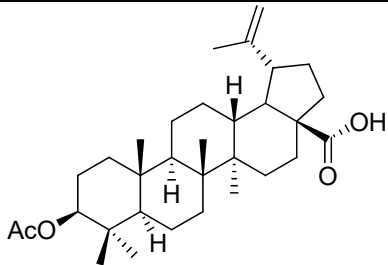
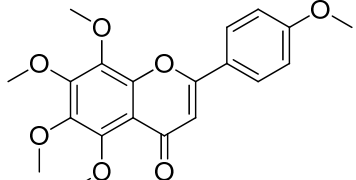
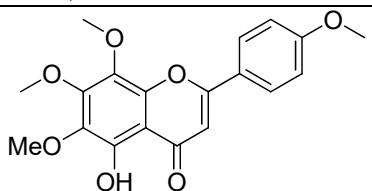
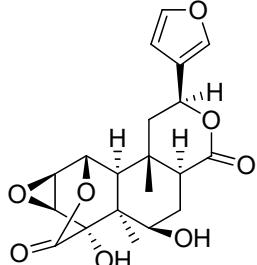
223		IN00272	532.43	81.9
224		IN00273	471.47	79.4
225 ^c	 Betulinic acid	IN00281	456.70	89.0
226		IN00282	889.03	110.8
227		IN00284	474.37	89.8
228		IN00285	272.30	89.1
229		IN00286	248.71	83.5
230		IN00287	140.09	76.8

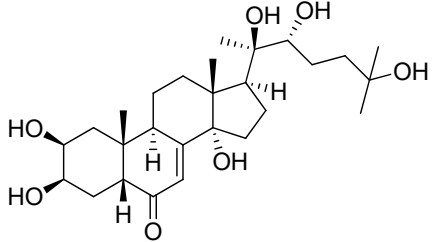
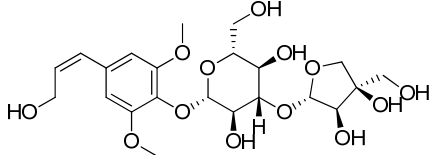
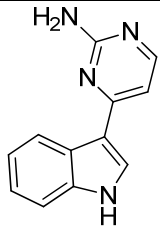
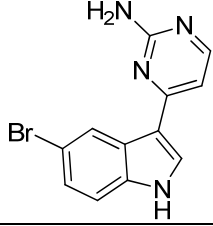
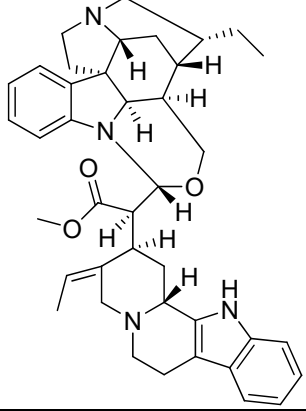
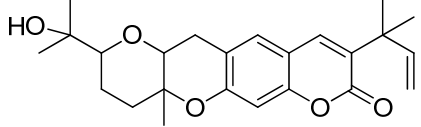
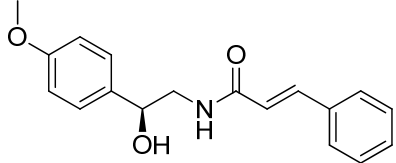
231		IN00288	368.47	70.6
232		IN00289	352.43	67.4
233		IN00290	232.23	93.9
234		IN00292	290.27	65.9
235		IN00293	324.37	111.8
236		IN00294	338.40	106.1
237		IN00295	268.26	75.9
238		IN00296	328.27	91.4

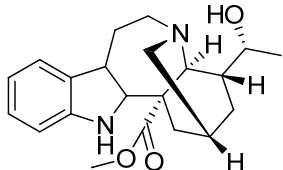
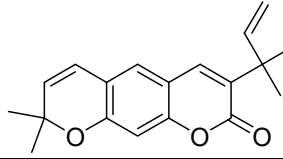
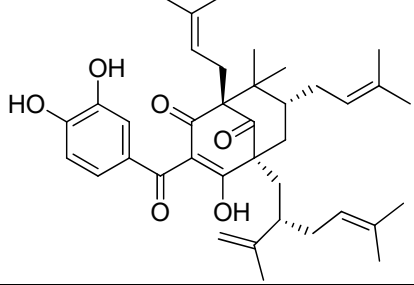
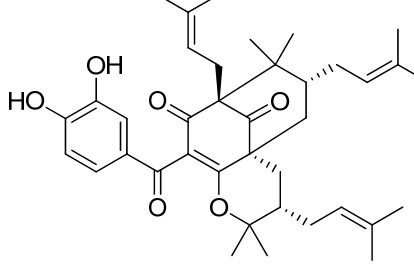
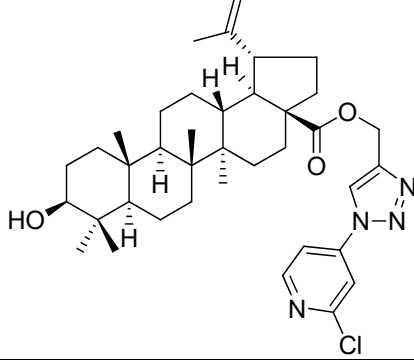
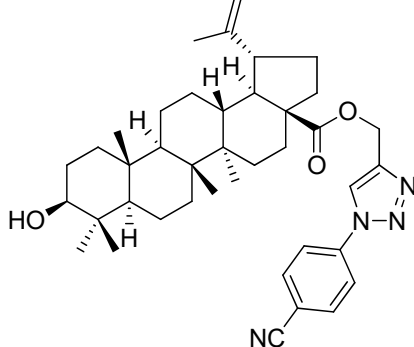
239		IN00297	256.25	86.7
240		IN00298	338.40	130.8
241		IN00299	294.30	146.5
242		IN00300	142.11	131.9
243		IN00301	192.21	135.9
244		IN00302	286.41	113.2
245	 2HCl	IN00303	553.56	124.6
246		IN00304	228.24	117.3
247 ^b	 Coumurrayin	IN00305	274.31	93.5

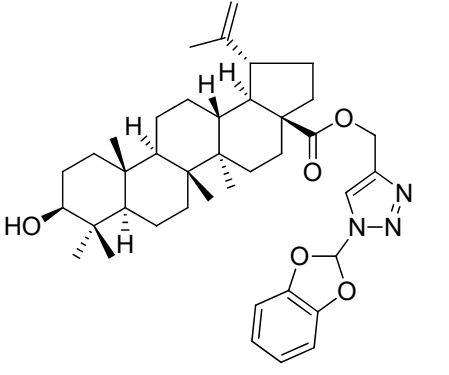
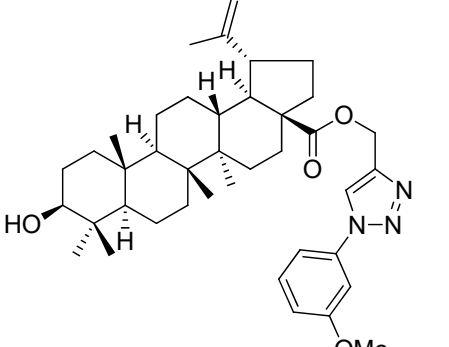
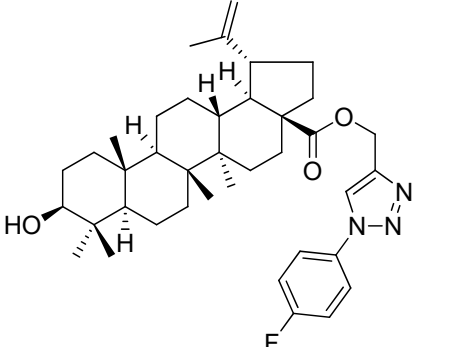
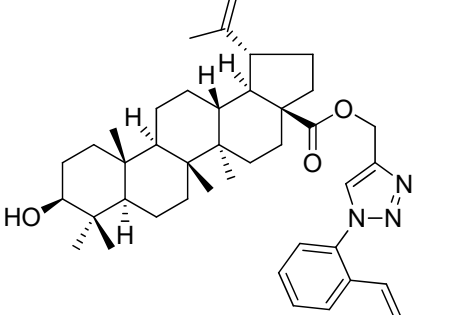
248		IN00306	362.42	98.7
249		IN00307	308.33	110.4
250		IN00308	424.40	99.5
251		IN00309	300.31	161.7
252		IN00310	258.27	124.9
253		IN00311	380.48	102.3

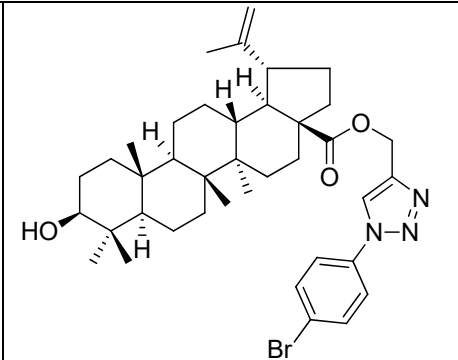
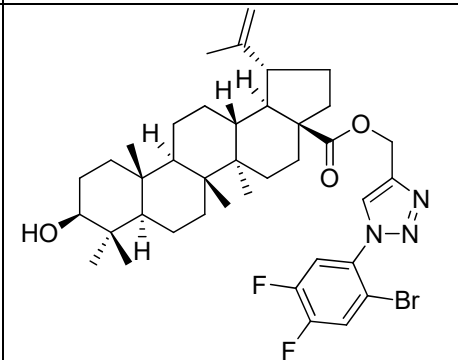
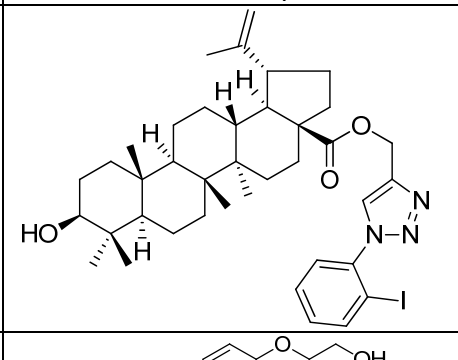
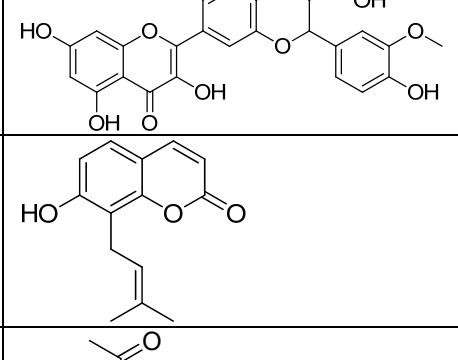
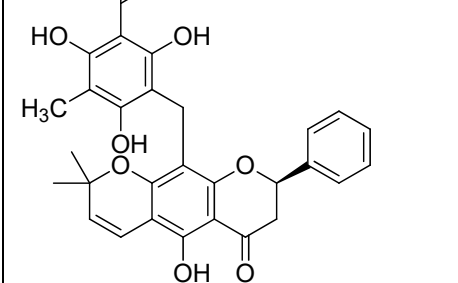
254		IN00312	410.12	142.7
255		IN00313	263.33	100.4
256		IN00314	354.35	118.1
257		IN00315	383.52	103.3
258		IN00316	416.42	104.0
259		IN00317	272.25	101.4
260		IN00318	370.40	100.7

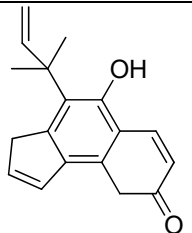
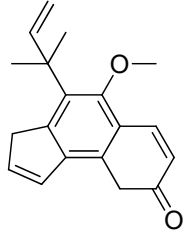
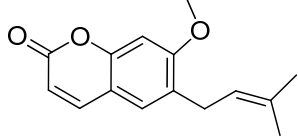
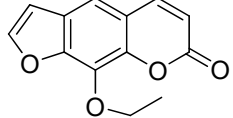
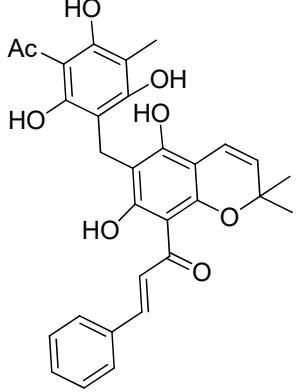
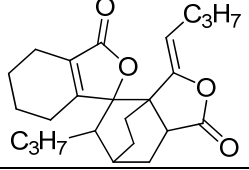
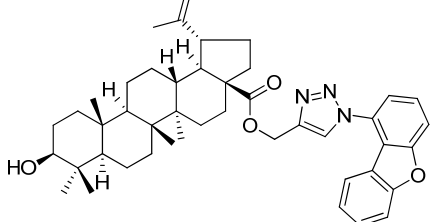
261		IN00319	342.28	129.3
262		IN00321	368.43	120.9
263 ^c	 Betulinic acid	IN00324	456.70	117.3
264		IN00325	498.74	101.9
265		IN00327	372.37	132.9
266	 MeO	IN00328	358.34	126.3
267		IN00329	390.38	94.3

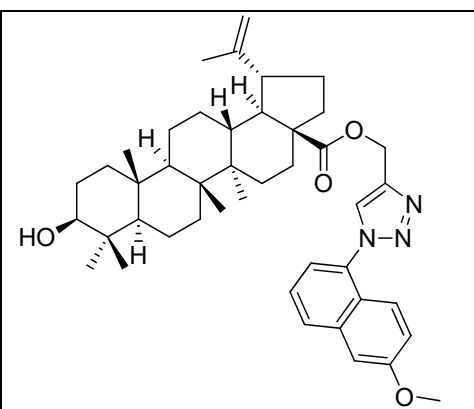
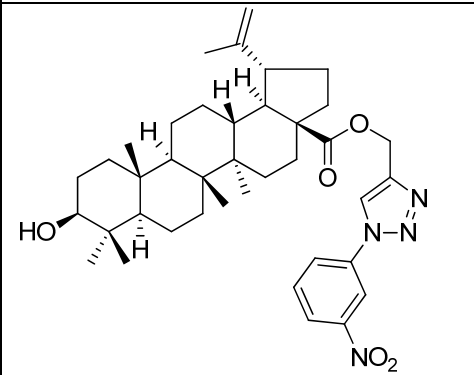
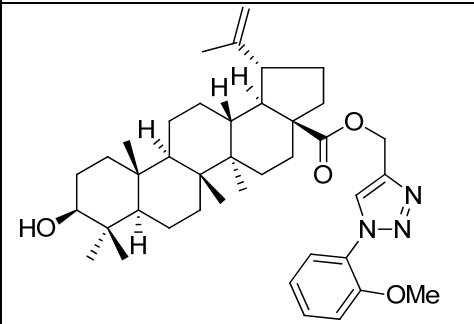
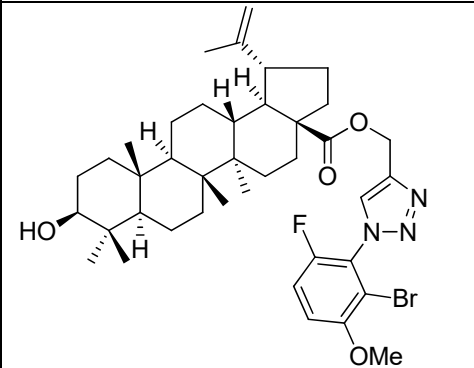
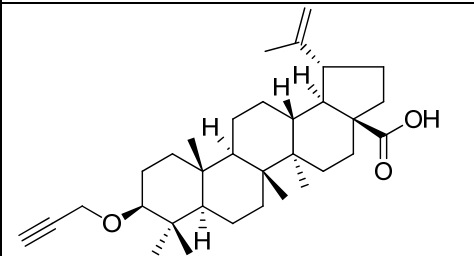
268		IN00330	480.63	101.5
269		IN00331	504.48	93.9
270		IN00332	210.23	95.7
271		IN00333	289.13	96.5
272		IN00336	632.83	102.7
273		IN00339	398.49	137.4
274		IN00340	297.35	97.4

275		IN00341	356.46	102.0
276		IN00343	228.24	161.9
277		IN00344	602.80	105.4
278		IN00345	602.80	83.5
279		IN00346	649.31	127.7
280		IN00347	638.88	111.9

281		IN00348	657.88	97.1
282		IN00349	643.90	115.9
283		IN00350	631.86	103.1
284		IN00351	639.91	107.6

285		IN00352	692.77	93.0
286		IN00353	728.75	98.2
287		IN00355	739.77	97.8
288		IN00357	478.45	106.2
289		IN00358	230.26	146.9
290		IN00359	516.54	137.9

291		IN00360	266.33	85.8
292		IN00361	280.36	105.0
293		IN00362	244.29	100.9
294		IN00363	230.22	90.4
295		IN00364	516.54	107.1
296		IN00365	384.51	129.5
297		IN00369	703.95	93.1

298		IN00371	693.96	88.4
299		IN00372	659.88	171.4
300		IN00373	643.90	114.8
301		IN00374	740.79	127.3
302		IN00380	494.75	114.8

^a This repository consists of natural products, plus semi-synthetic derivatives along with few synthetic small molecules.

^b IN00236 and IN00305 codes belong to the same compound 'coumurrayin'. These were submitted two times to the IIIM NP repository, therefore have two different codes. They differ from each other only in terms of their purity. IN00236 is 92% pure whereas IN00305 is 95% pure.

^c IN00281 and IN00324 codes belong to the same compound 'betulinic acid'. These were submitted two times to the IIIM NP repository, therefore have two different codes. They differ from each other only in terms of their purity. IN00280 is 92% pure whereas IN00322 is 96% pure.